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Parker

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(54) **ASSESSING NEURAL STATE FROM ACTION POTENTIALS**

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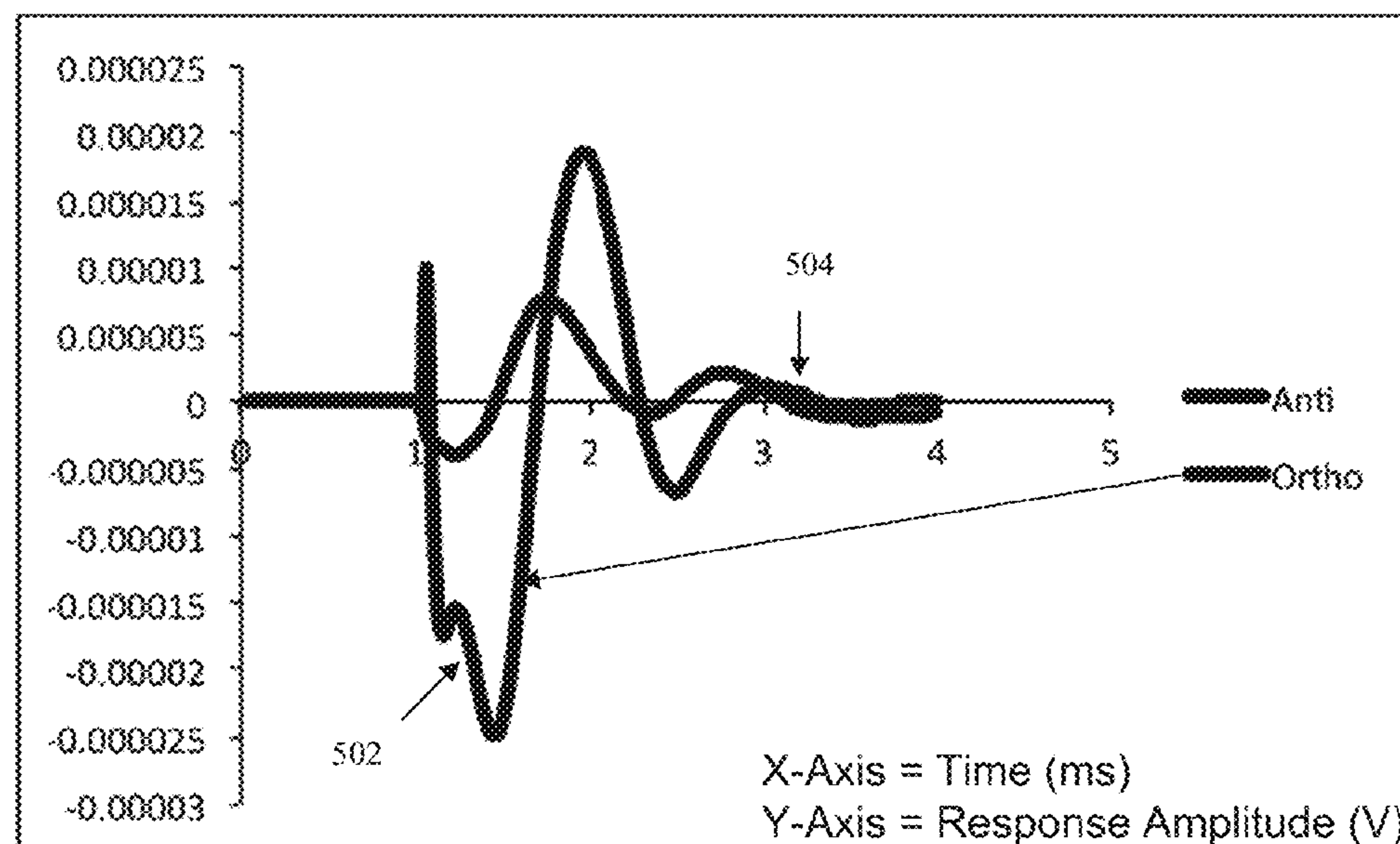
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(57) **ABSTRACT**

The neural health or state of a subject is assessed. A recording is obtained of a compound action potential arising in neural tissue of the subject. The recording is processed to determine whether a profile of the recorded compound action potential is anomalous, such as by exhibiting doublets, peak broadening or deformation, or other anomaly. An indication is output regarding the neural state of the subject based on determined anomalies in the recorded compound action potential.

20 Claims, 9 Drawing Sheets



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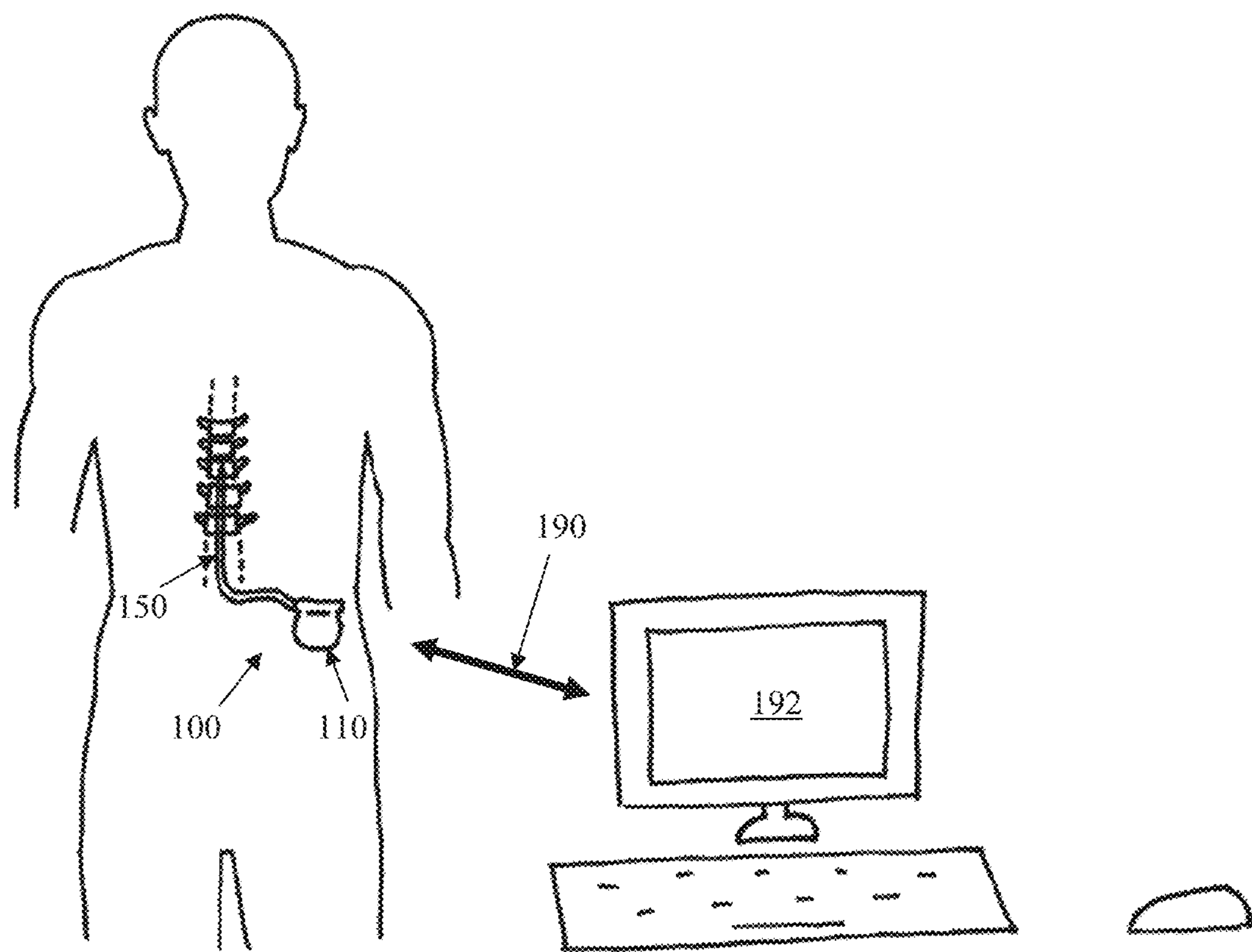


Figure 1a

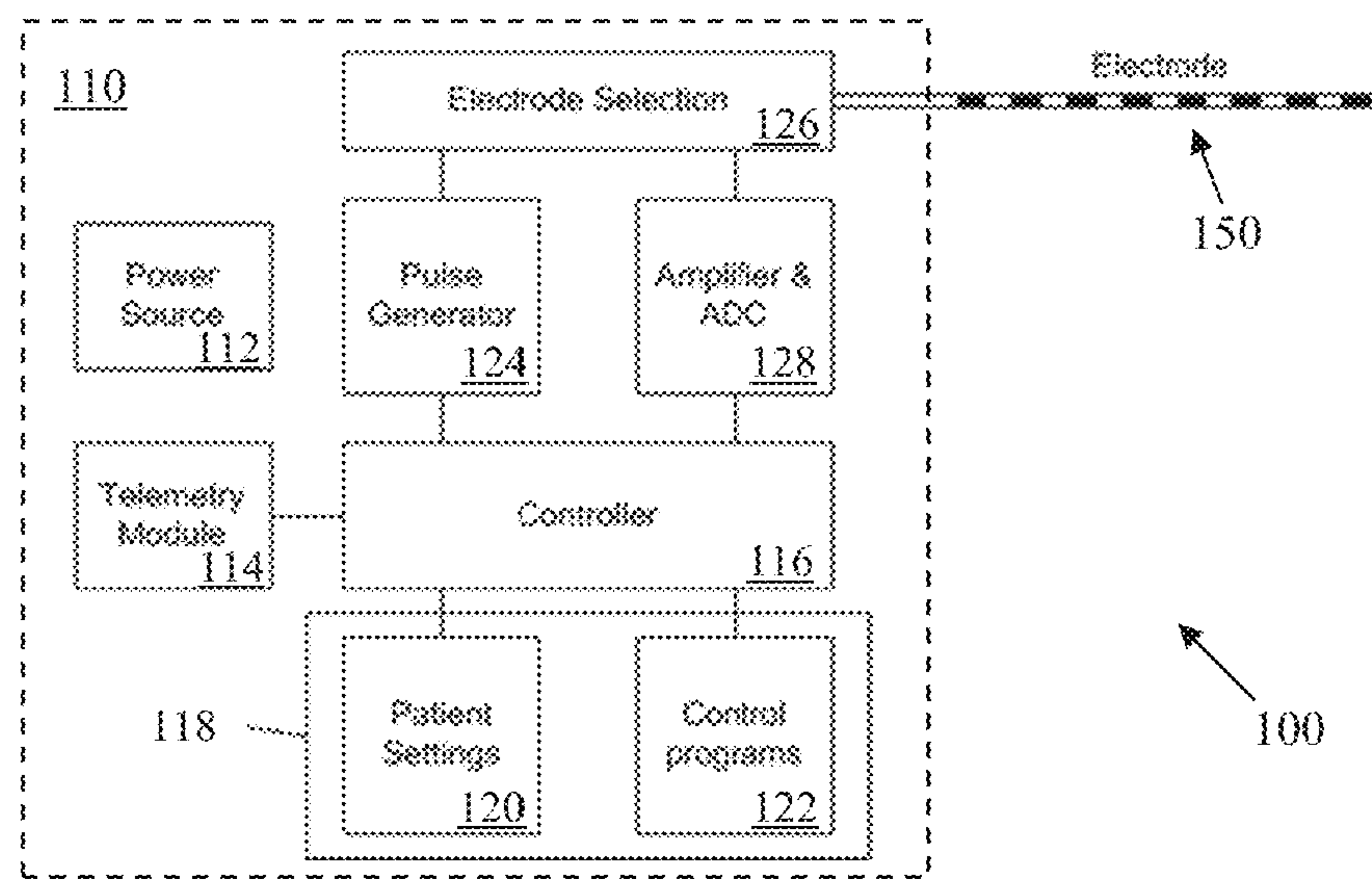


Figure 1b

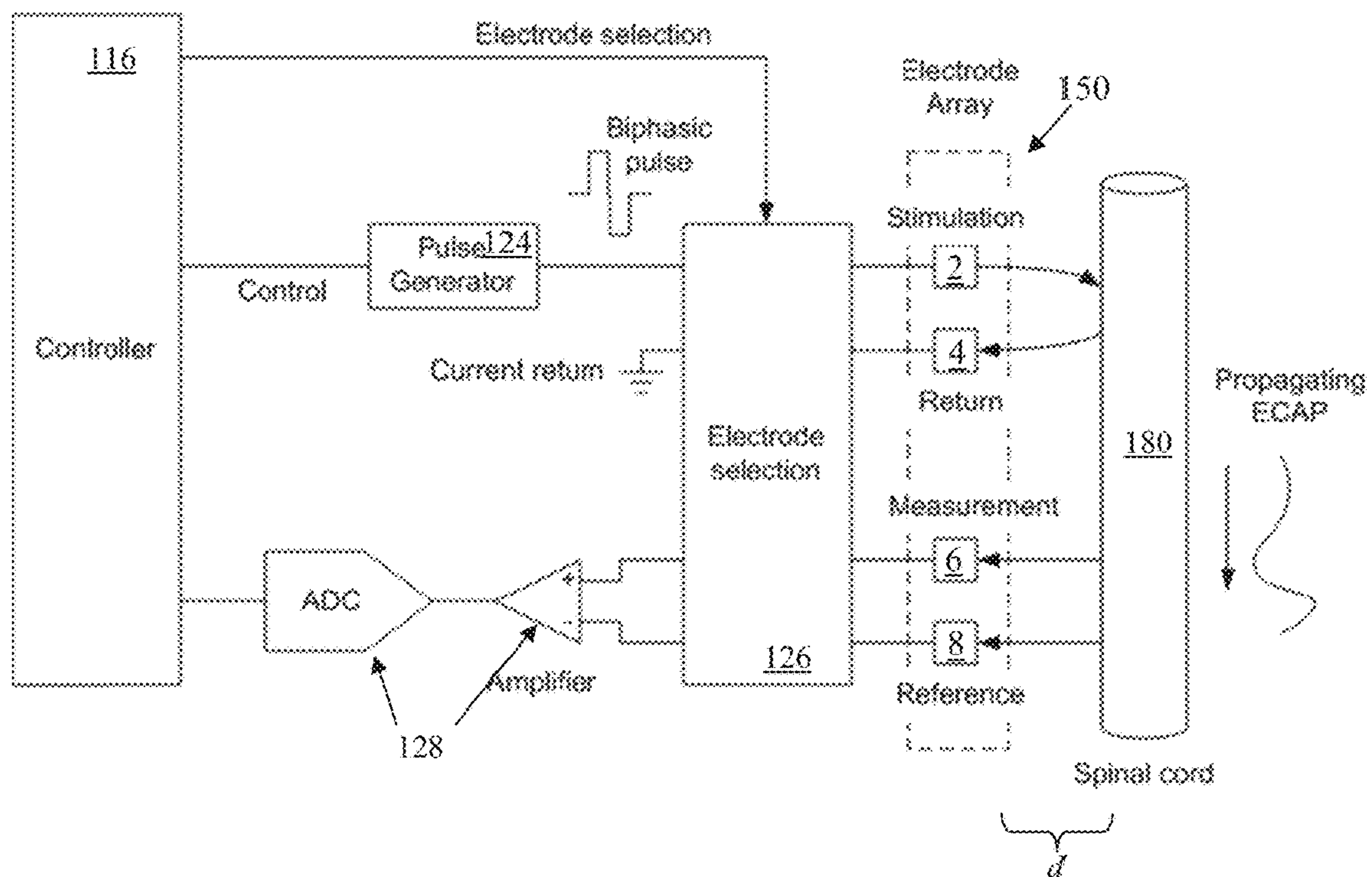


Figure 1c

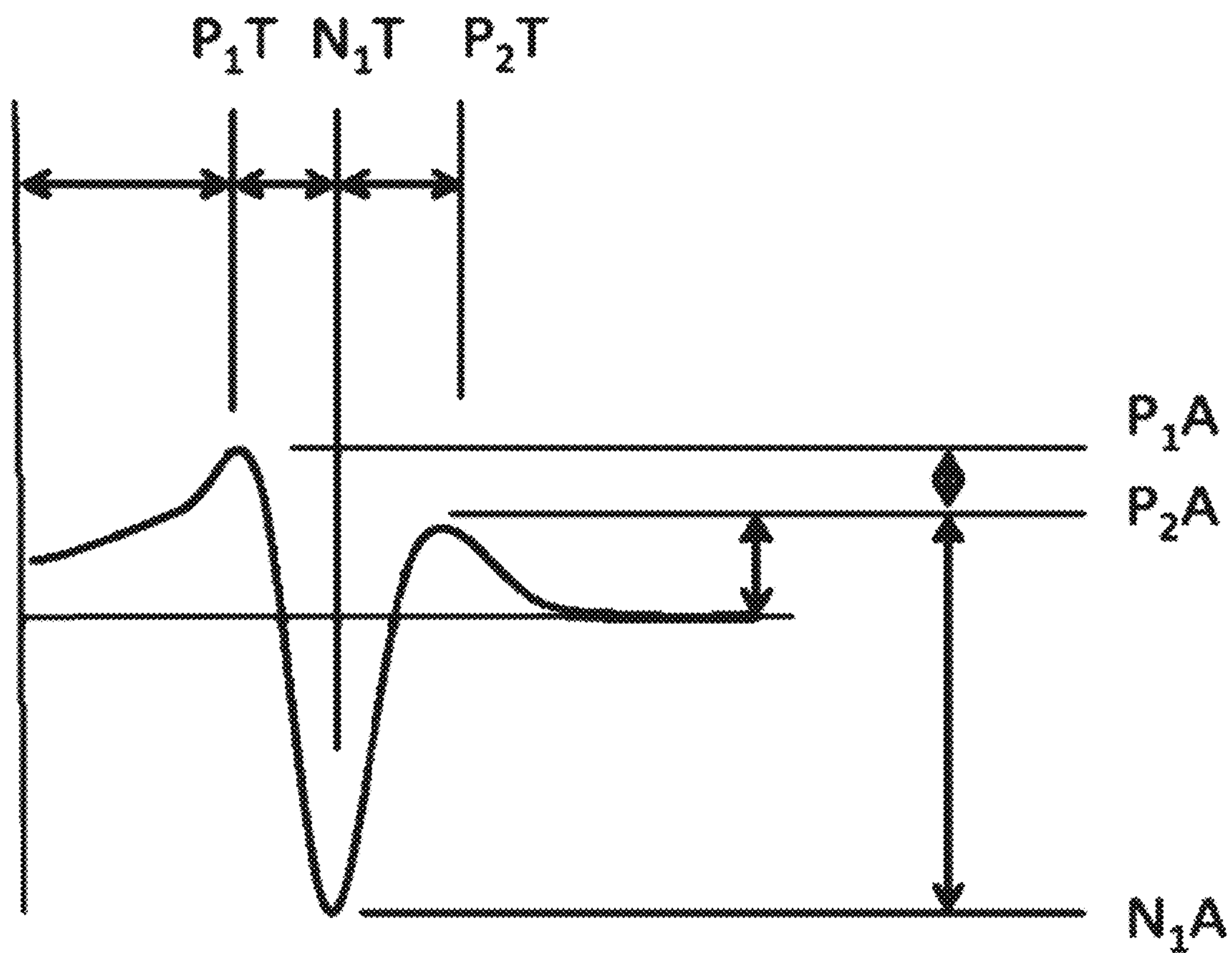


Figure 2a

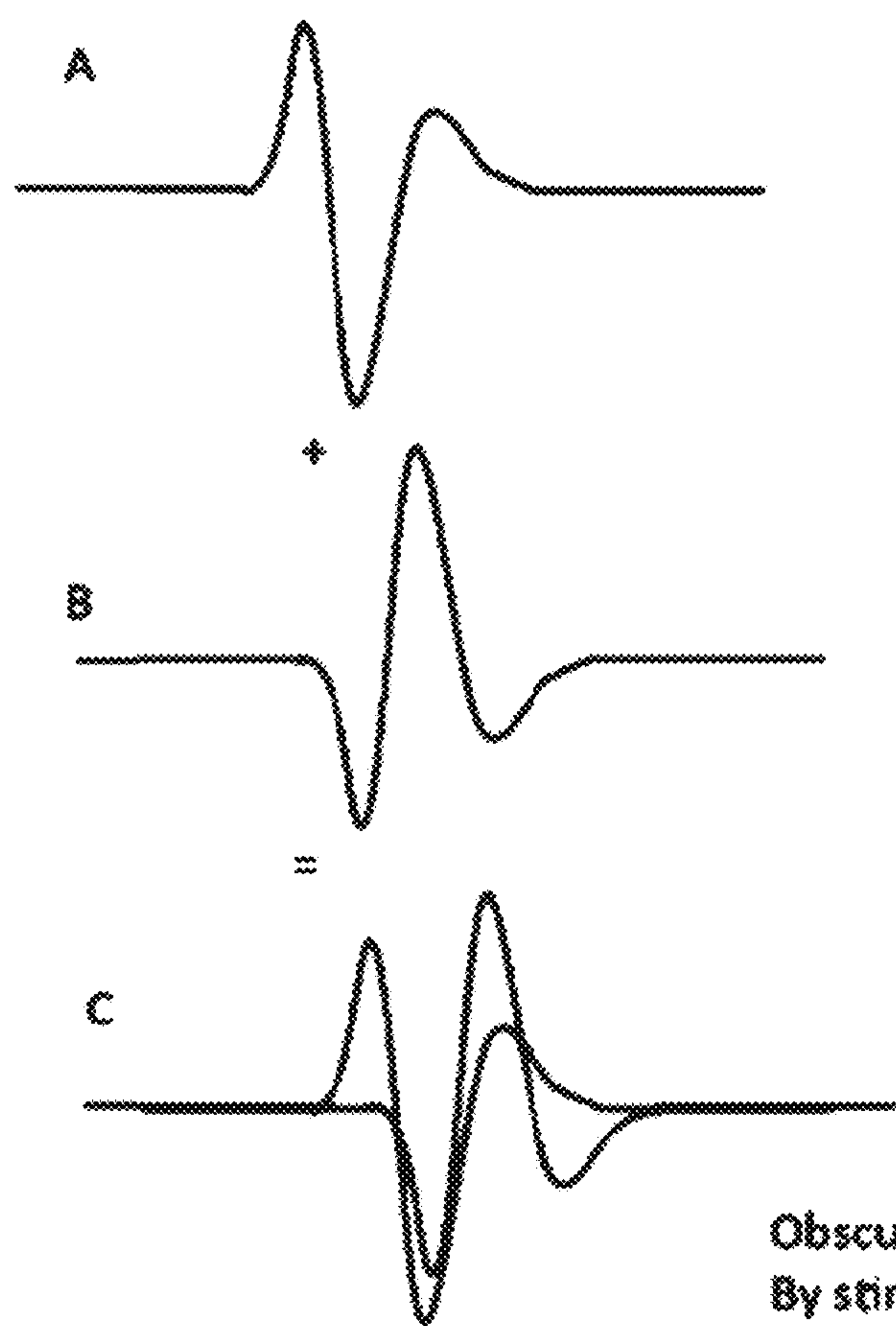


Figure 2b

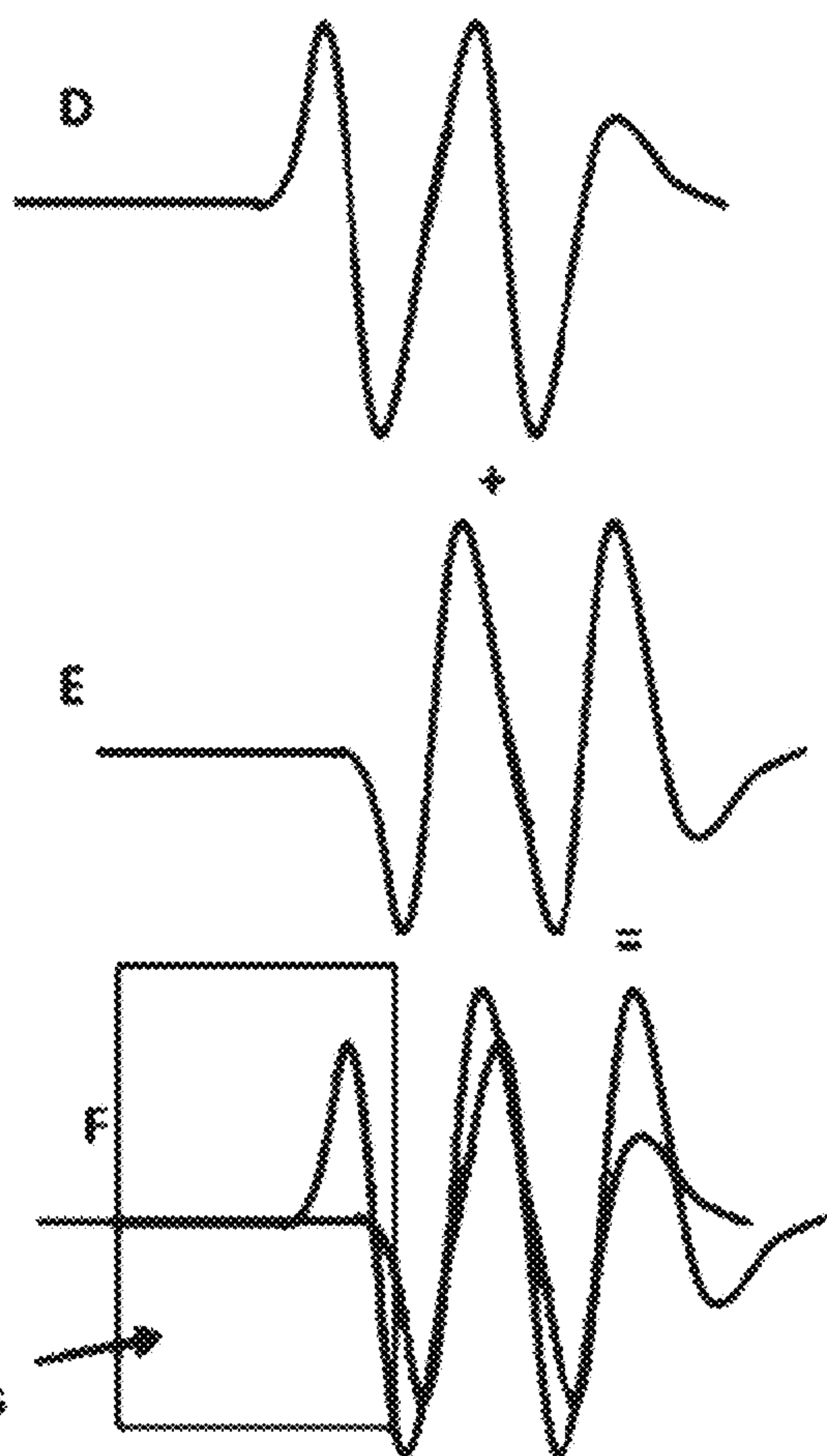


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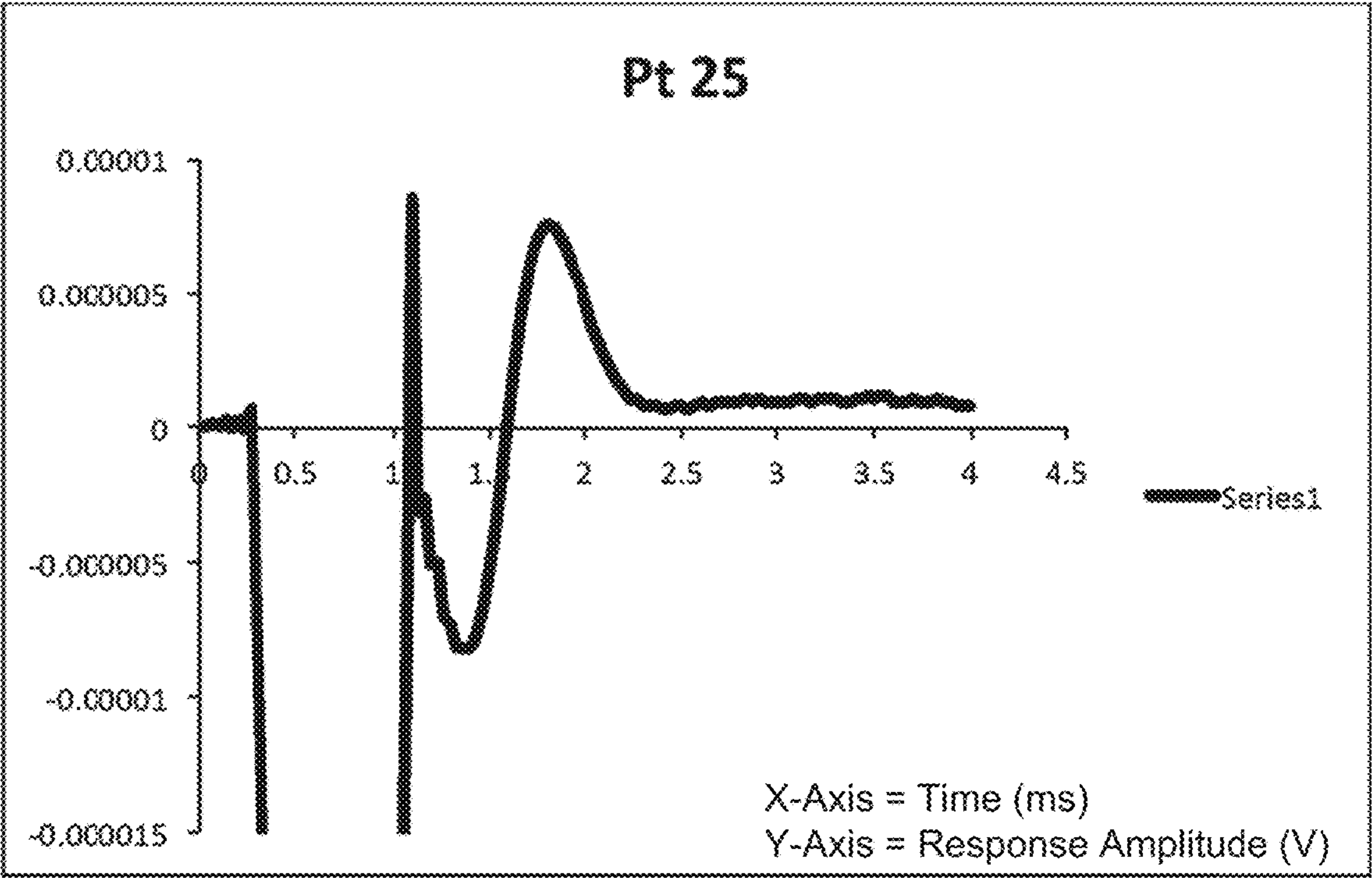


Figure 3

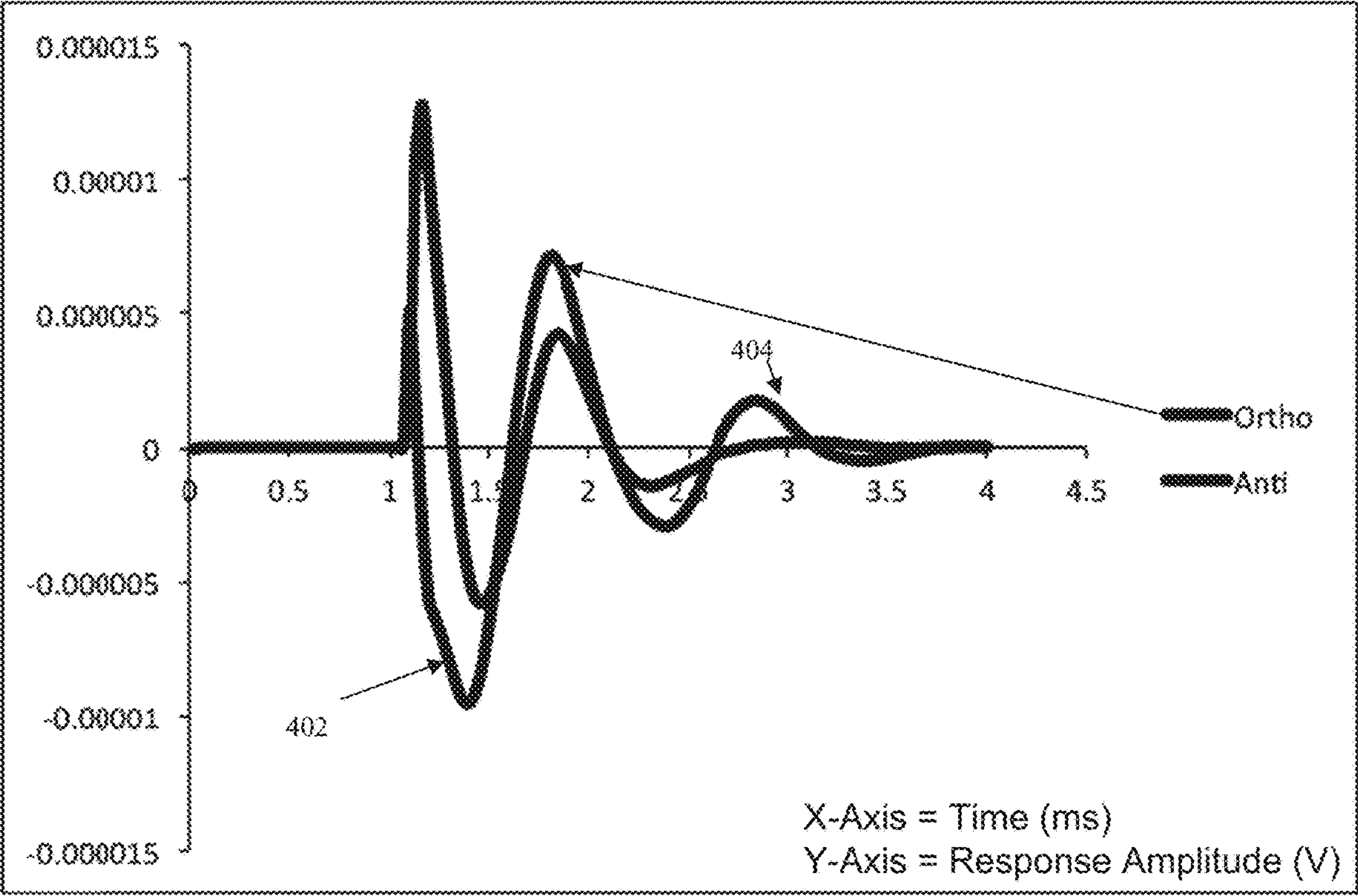


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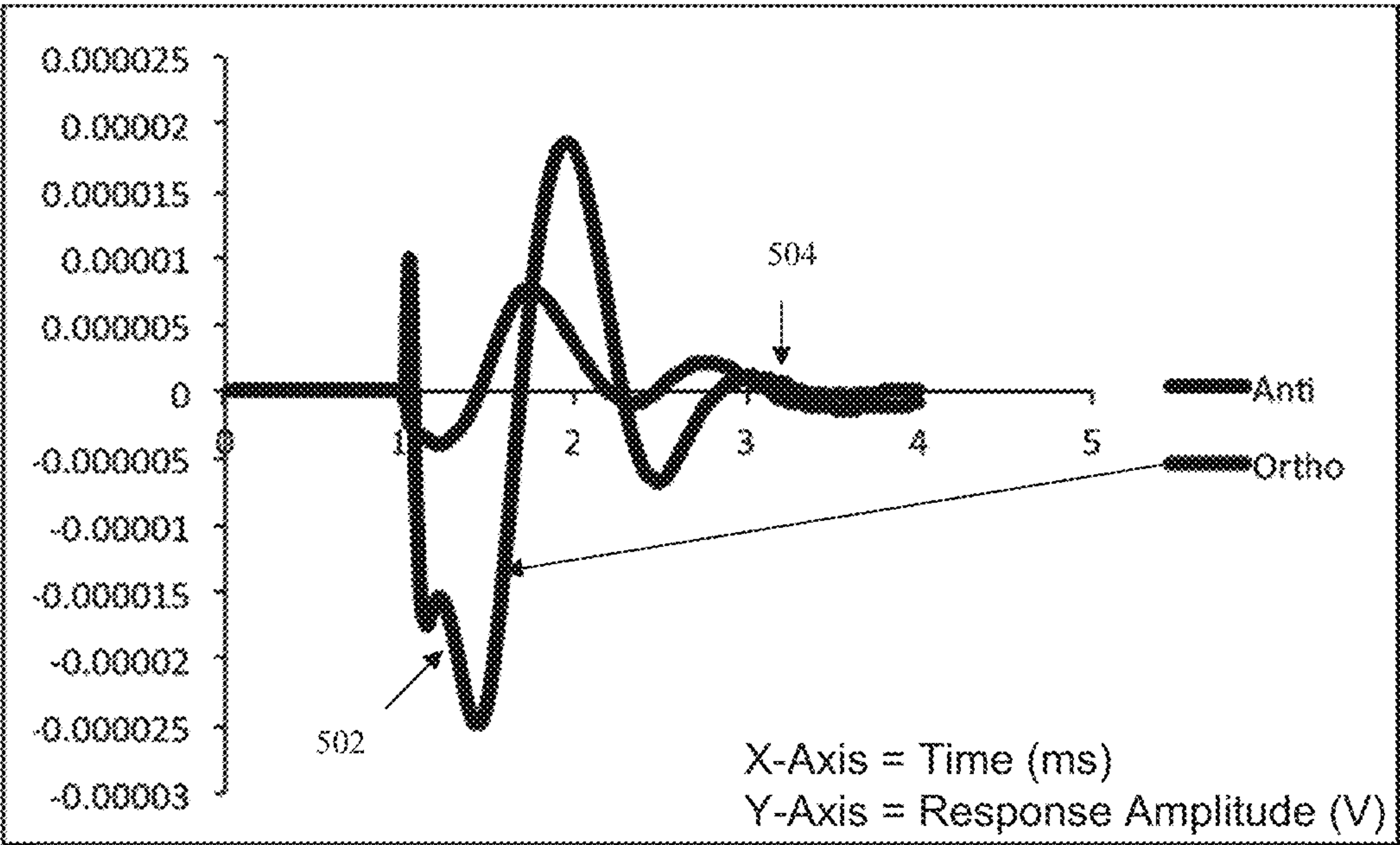


Figure 5

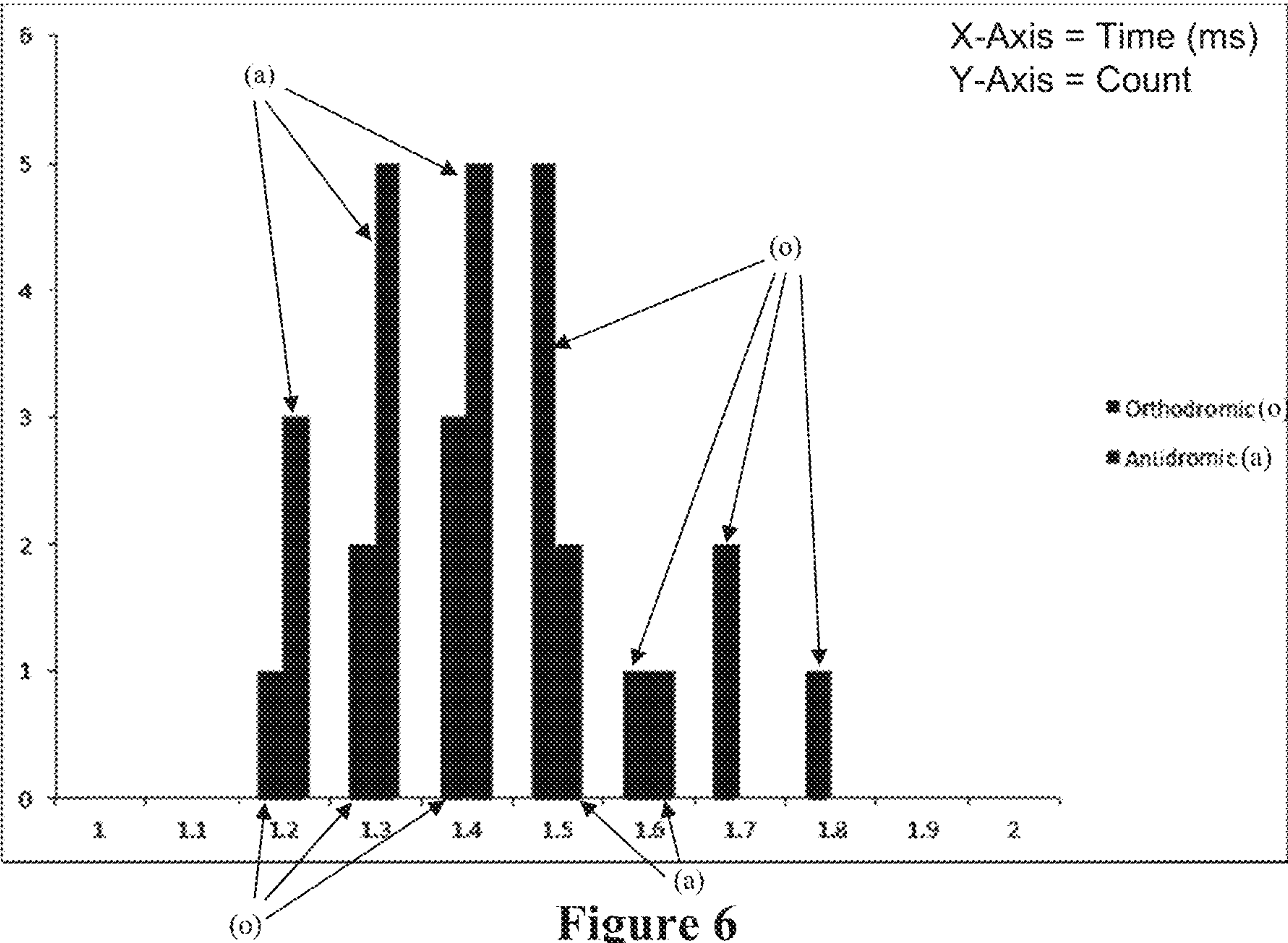


Figure 6

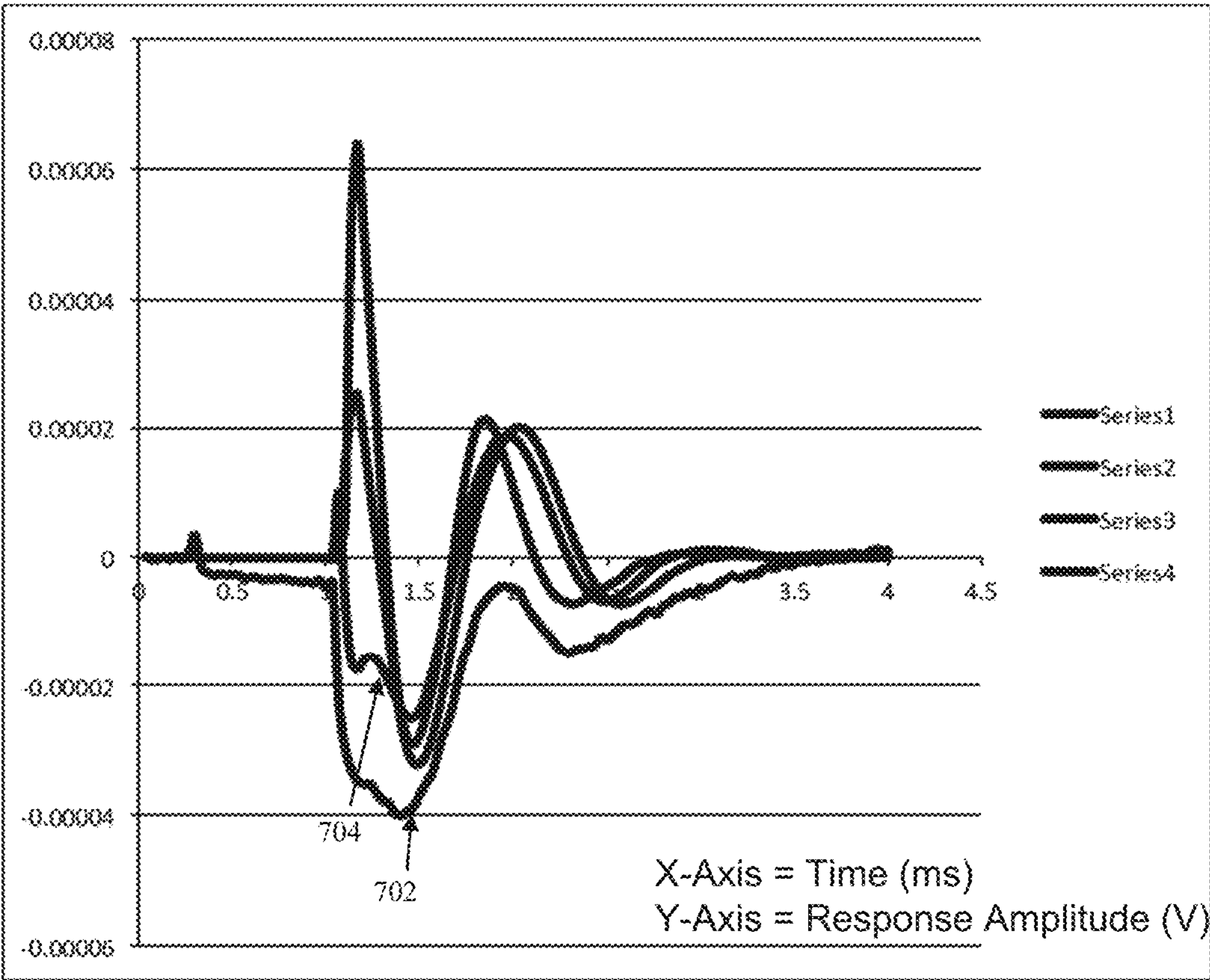


Figure 7

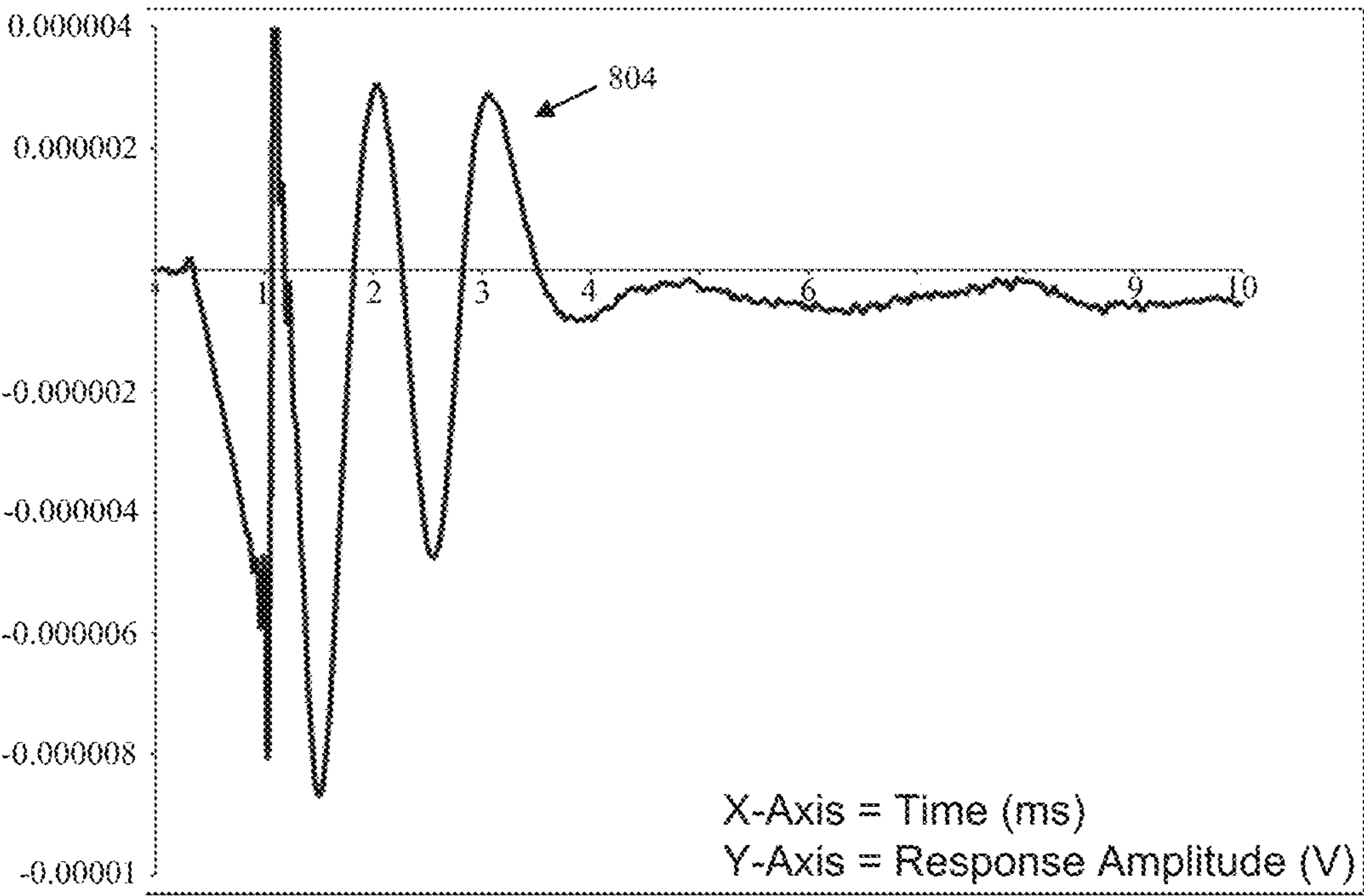


Figure 8

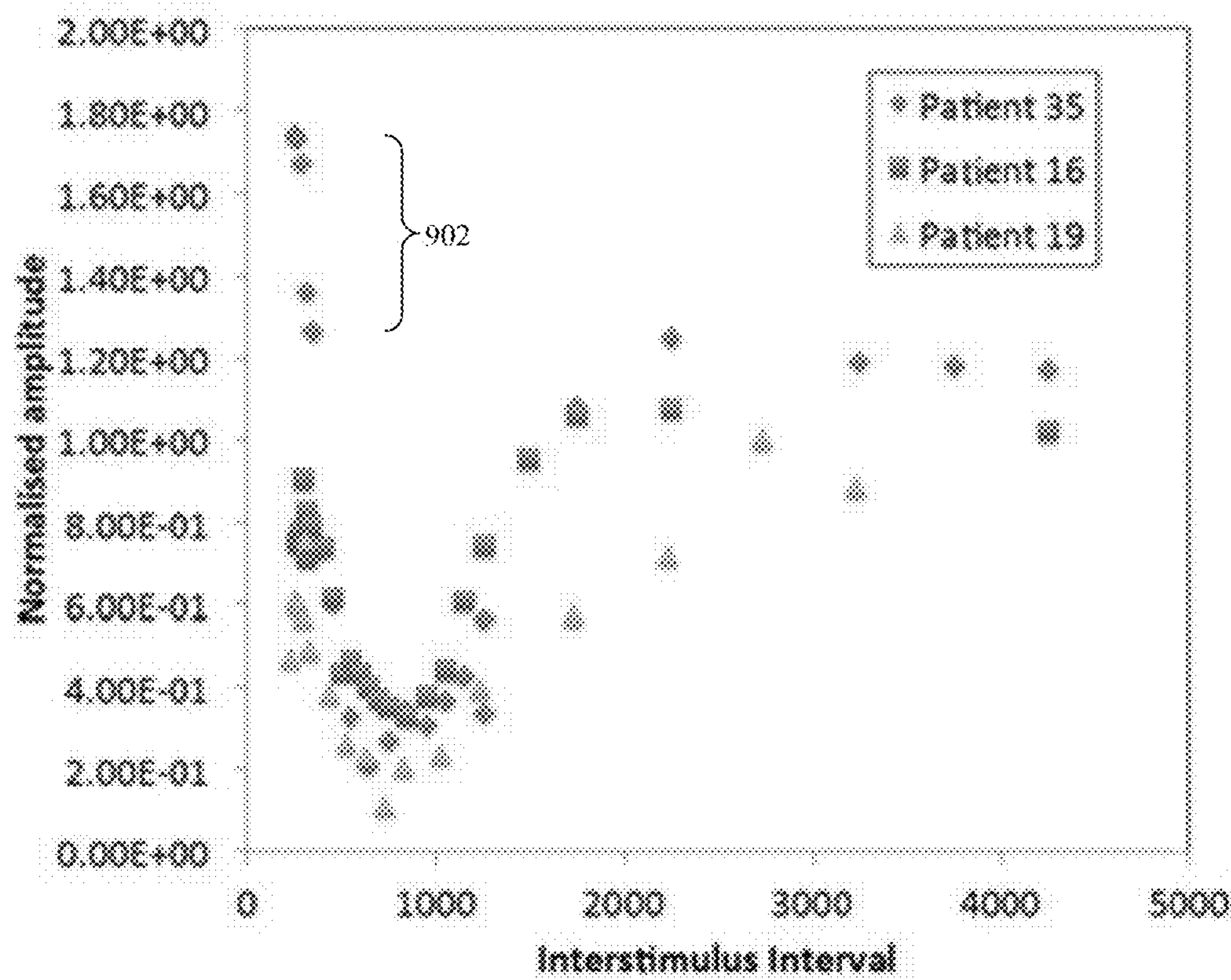


Figure 9

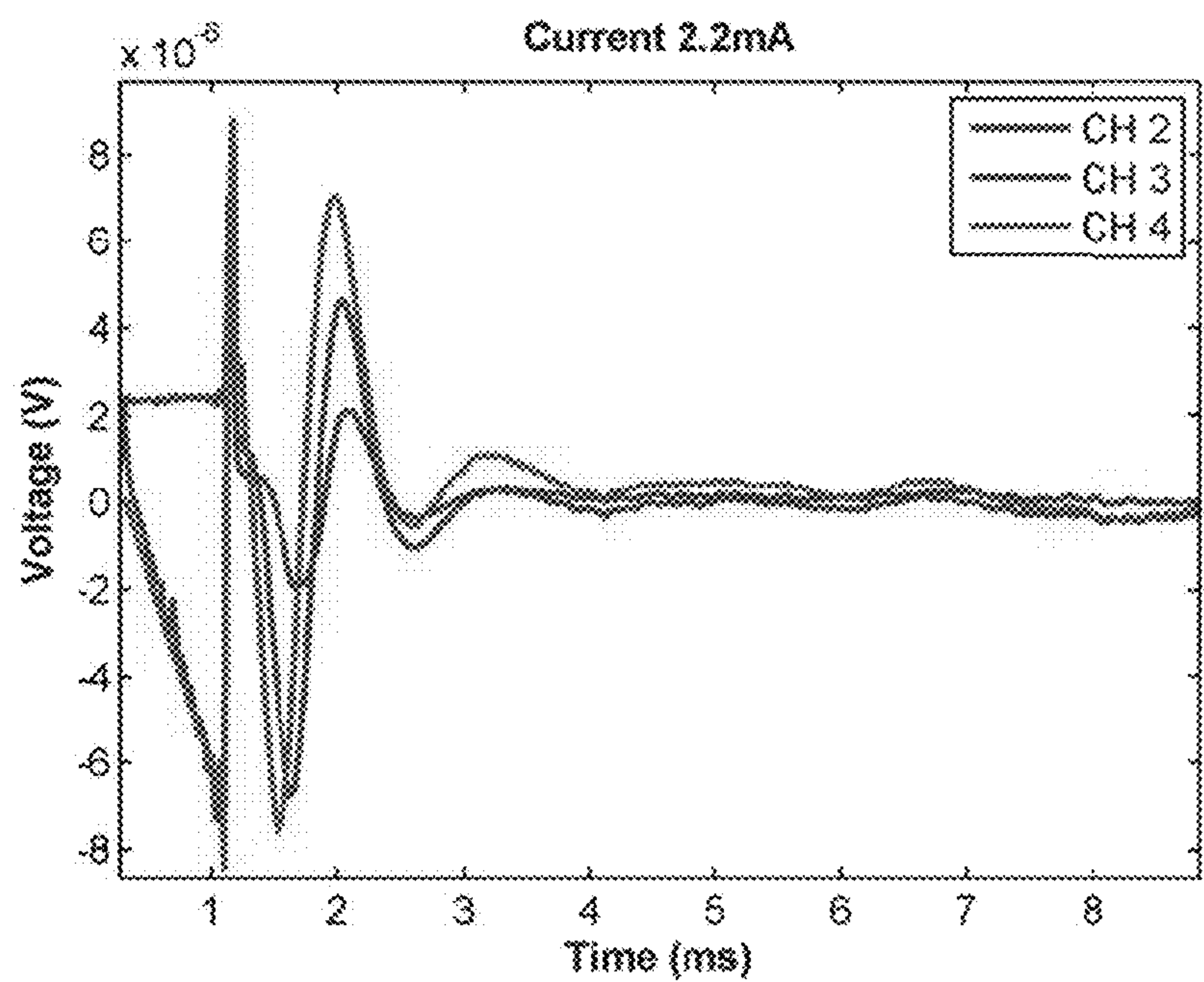


Figure 10

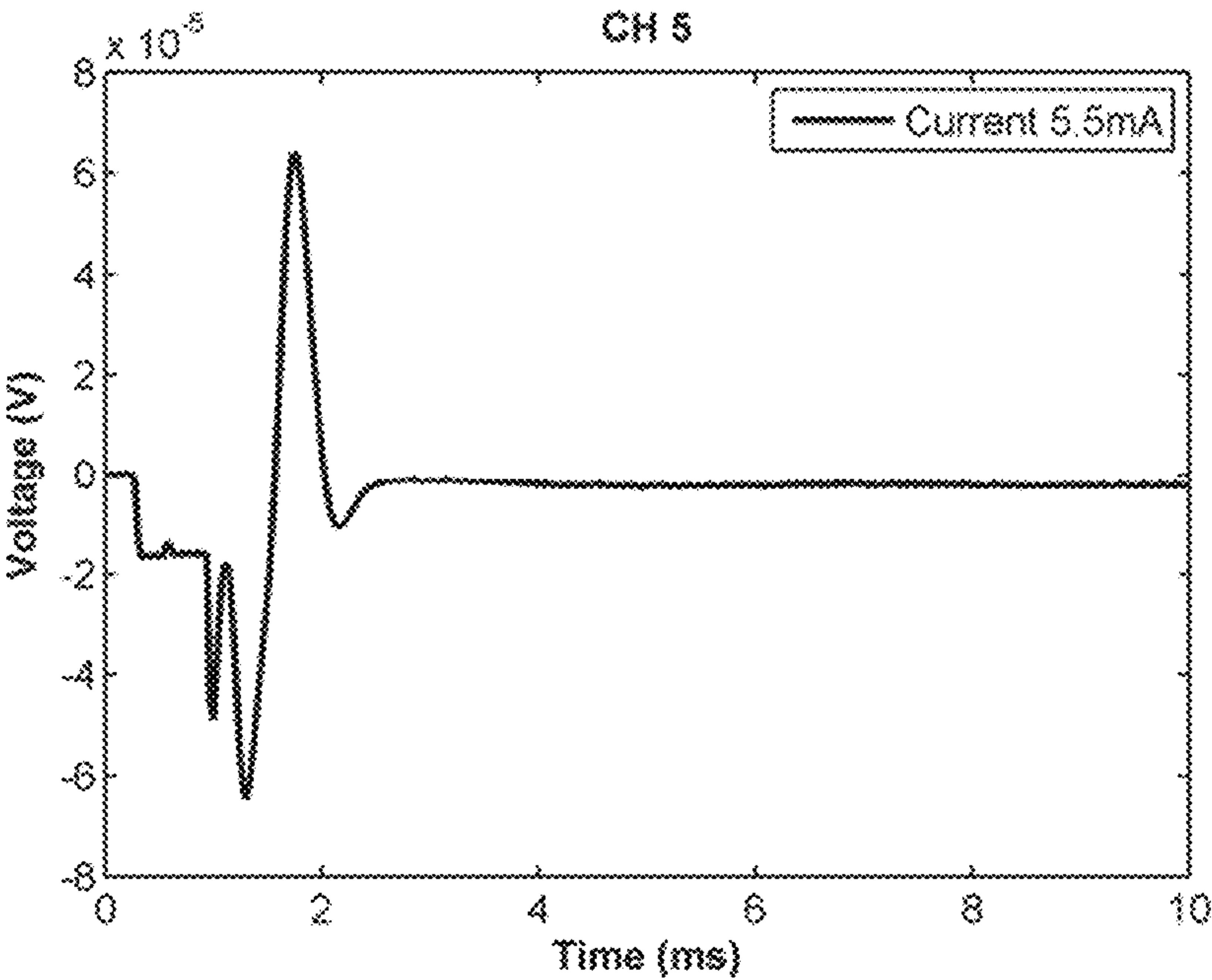


Figure 11

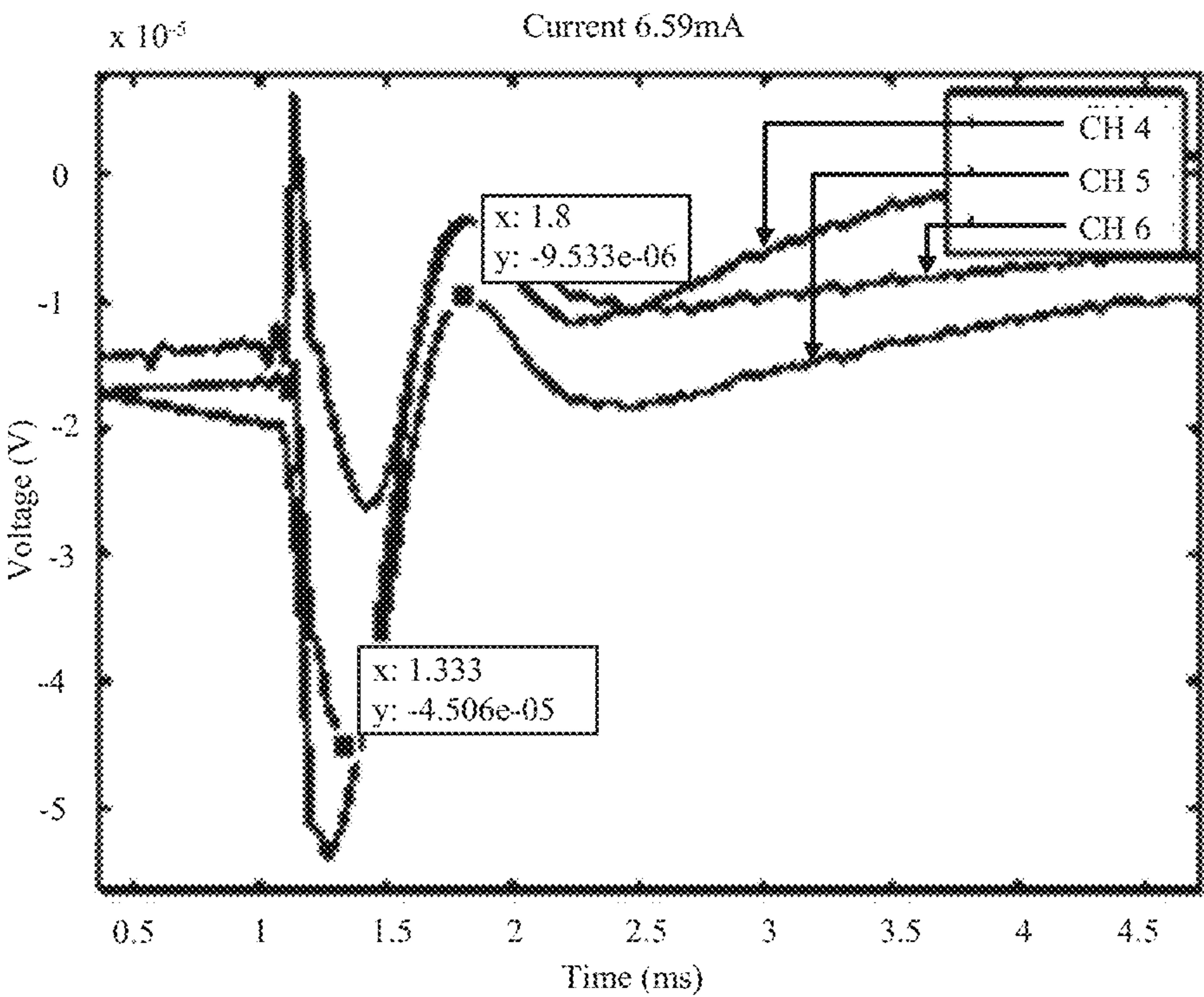


Figure 12

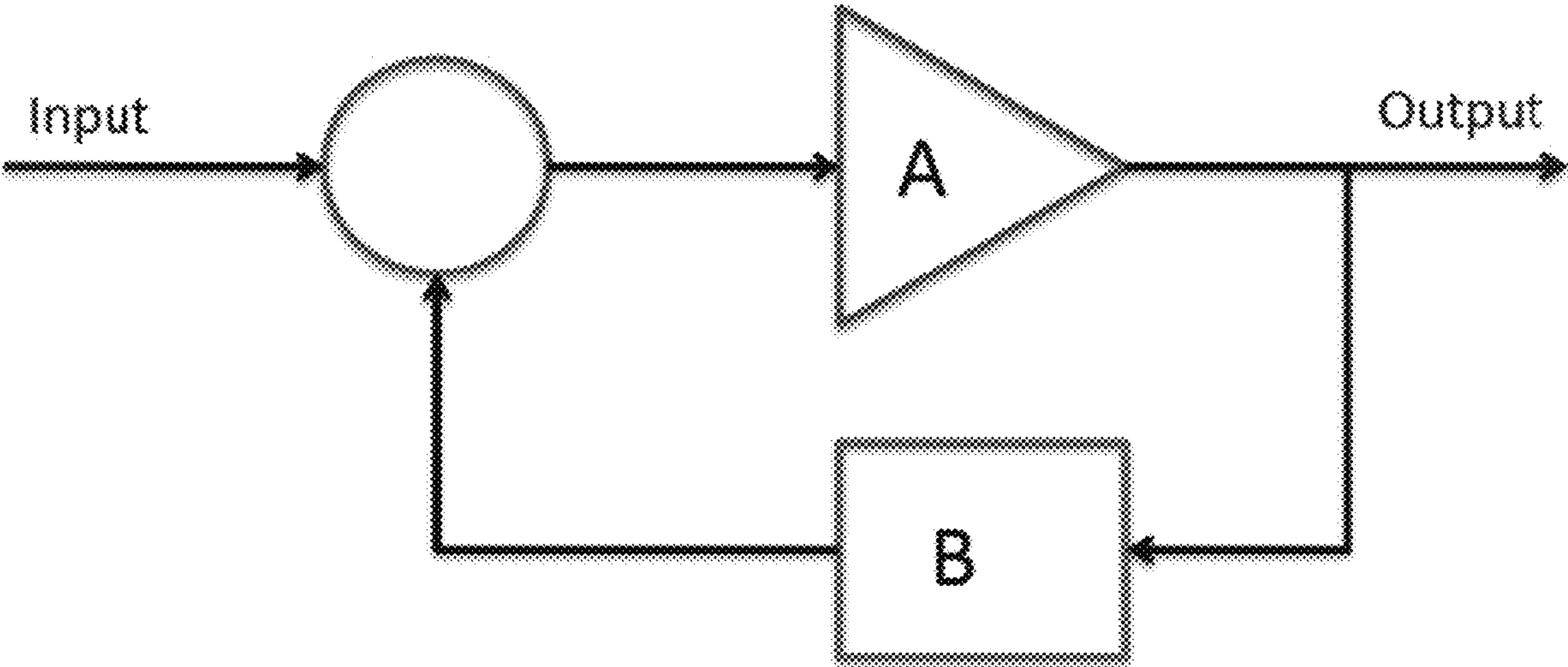


Figure 13

ASSESSING NEURAL STATE FROM ACTION POTENTIALS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/129,407 entitled "Assessing Neural State from Action Potentials", filed Sep. 26, 2016 which is a national stage of PCT Application No. PCT/AU2015/050135 filed Mar. 27, 2015 which claims the benefit of Australian Provisional Patent Application No. 2014901110 filed Mar. 28, 2014, the disclosures of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

The present invention relates to assessing a neural state from neural potentials, and in particular relates to obtaining a recording of a neural potential arising on neural tissue, and monitoring for an anomalous profile of the recording, in order to assess the existence, state or progress of a neural disease.

BACKGROUND OF THE INVENTION

Neuropathic pain arises from damage or disease affecting the somatosensory system, and may result from disorders of the peripheral nervous system or the central nervous system. For example, complex regional pain syndrome (CRPS) is a severe type of pain disorder.

There is no known single pathognomonic symptom or sign of neuropathic disease. Consequently, it is difficult to diagnose neuropathic disease and to monitor the progress of neuropathic disease. No conclusive objective diagnostic exists for neuropathic pain, and clinicians must rely largely on a subjective clinical observation of the patient's responses. Neuropathic pain is also difficult to treat and often responds poorly to standard pain treatments.

A range of medications for treating neuropathic pain exist, including gabapentin for example. Careful documentation and appropriate monitoring of treatment are important for the safe and effective use of such medications, however this is difficult to achieve due to the difficulty of determining the disease state or monitoring the progress of the disease or symptoms. Advanced therapies for treating neuropathic pain include spinal cord stimulation.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

In this specification, a statement that an element may be "at least one of" a list of options is to be understood that the element may be any one of the listed options, or may be any combination of two or more of the listed options.

SUMMARY OF THE INVENTION

According to a first aspect the present invention provides a method of assessing a neural state of a subject, the method comprising:

- obtaining a recording of a compound action potential arising in neural tissue of the subject;
- processing the recording to determine whether a profile of the recorded compound action potential is anomalous;
- and
- outputting an indication regarding the neural state of the subject based on determined anomalies in the recorded compound action potential.

A method for determining whether a human patient has neuropathic disease, comprising:

- obtaining a recording of a compound action potential arising in neural tissue of the patient; and
- diagnosing the patient as having neuropathic disease if a profile of the recorded compound action potential is anomalous.

A non-transitory computer readable medium for assessing a neural state of a subject, comprising instructions which, when executed by one or more processors, causes performance of the following:

- obtaining a recording of a compound action potential arising in neural tissue of the subject;
- processing the recording to determine whether a profile of the recorded compound action potential is anomalous;
- and
- outputting an indication regarding the neural state of the subject based on determined anomalies in the recorded compound action potential.

The detection of irregularities or anomalies in the recorded response may comprise any one or more of:

- determining whether more than three peaks exist in the recorded compound action potential;
- determining whether a peak in the recorded compound action potential is unexpectedly broad;
- determining whether a peak in the recorded compound action potential has an atypically swift rate of rise;
- determining whether anomalous frequency components exist in the recorded compound action potential when assessed in the frequency domain;
- determining a degree of deviation of the recorded compound action potential from a predefined expected response profile and, if the degree of deviation exceeds a predetermined threshold, indicating that the recorded response is anomalous.

Some embodiments may determine whether more than three peaks exist in the recorded compound action potential by measuring an amplitude or power of the recorded compound action potential in a time window positioned after cessation of a normal response. The amplitude or power of the recorded compound action potential in such a time window can be used to assess the presence or absence of an abnormal response arising later than a normal P2 peak. Additionally or alternatively, a matched filter or other signal processing means may be used to detect the presence of an extra lobe in the recorded compound action potential.

Some embodiments of the present invention thus recognise that when considering a recorded compound action potential (CAP) obtained from a person suffering from an altered neural state such as CRPS, rather than the CAP taking a typical three lobed profile, lobe deformation or additional lobes referred to herein as doublets can be observed to arise in the ECAP. Moreover, the degree of lobe deformation and/or the relative size of the additional lobes

appearing in the response can be measured, in order to give not only a binary diagnosis but also a quantitative measure of the severity of the disease suffered by the person. Absence of such response profile anomalies may be used to eliminate some diseases from a diagnosis for the person. Repeated assessment of the recorded response profile from time to time, for example throughout administration of a therapy, may be used to assess disease state, disease progress, and therapy efficacy, and may be used to guide therapy modifications and optimisation over time. Therapy modifications may include modifications of dosage of a medicament and/or modification of a stimulus regime applied by a spinal column stimulator.

Accordingly, the present invention recognises that monitoring for the occurrence and severity of anomalies such as doublets in the recorded response profile gives a diagnostic for neuropathic pain or neural damage or in general any neural disease which gives rise to atypical neural response profiles.

Notably, some embodiments of the present invention further recognise that when application of a stimulus to a first neural site gives rise to anomalies in a recorded neural response profile, application of the same stimulus to an alternative neural site might give rise to a recorded neural response without abnormalities. Such embodiments may thus provide for identifying a locus of neuropathic pain.

The method of the present invention may in some embodiments be performed intra-operatively for example to effect electrode array implantation site optimisation. The method of the present invention may additionally or alternatively be performed during an implant programming stage in order to optimise electrode selection to a site at which a locus of neuropathic pain is identified.

The invention may further provide for intra-operative monitoring of the response profile during a sympathectomy procedure, in order to provide an intra-operative progressive indication of efficacy of the sympathectomy.

According to a further aspect the present invention provides a method of treating a neural disease, the method comprising:

- ordering or requesting the result of the method of the first aspect; and
- administering or modifying a therapy in a manner responsive to the ordered result.

The compound action potential may arise from deliberate stimulation, whether peripheral stimulation or direct spinal column stimulation, for example.

BRIEF DESCRIPTION OF THE DRAWINGS

An example of the invention will now be described with reference to the accompanying drawings, in which:

FIG. 1a schematically illustrates an implanted spinal cord stimulator suitable for implementing the present invention;

FIG. 1b is a block diagram of the implanted neurostimulator;

FIG. 1c is a schematic illustrating interaction of the implanted stimulator with a nerve;

FIG. 2a illustrates the typical form of an electrically evoked compound action potential of a healthy subject, and FIGS. 2b and 2c illustrate how the CAP manifests in the recording when using a differential recording arrangement with an epidural ground;

FIG. 3 illustrates an actual ECAP recording obtained from a subject having a normal neural state;

FIG. 4 illustrates anomalous ECAP recordings obtained from a subject suffering a neural disease;

FIG. 5 illustrates anomalous ECAP recordings obtained from another subject suffering a neural disease;

FIG. 6 is a plot of the differences between the N1, N2 peaks measured doublets;

FIG. 7 shows the normalised antidromic responses from three patients plotted together;

FIG. 8 shows an example of a large doublet response in the antidromic response of one patient;

FIG. 9 is a plot of the normalized masker probe results for the refractory period of three patients;

FIGS. 10-12 illustrate the relative severity of doublet formation for three respective patients; and

FIG. 13 illustrates a control system by which a therapy may be modified in accordance with one embodiment of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. 1 schematically illustrates an implanted spinal cord stimulator **100** suitable for implementing the present invention. Stimulator **100** comprises an electronics module **110** implanted at a suitable location in the patient's lower abdominal area or posterior superior gluteal region, and an electrode assembly **150** implanted within the epidural space and connected to the module **110** by a suitable lead. Numerous aspects of operation of implanted neural device **100** are reconfigurable by an external control device **192**. Moreover, implanted neural device **100** serves a data gathering role, with gathered data being communicated to external device **192**.

FIG. 1b is a block diagram of the implanted neurostimulator **100**. Module **110** contains a battery **112** and a telemetry module **114**. In embodiments of the present invention, any suitable type of transcutaneous communication **190**, such as infrared (IR), electromagnetic, capacitive and inductive transfer, may be used by telemetry module **114** to transfer power and/or data between an external device **192** and the electronics module **110**.

Module controller **116** has an associated memory **118** storing patient settings **120**, control programs **122** and the like. Controller **116** controls a pulse generator **124** to generate stimuli in the form of current pulses in accordance with the patient settings **120** and control programs **122**. Electrode selection module **126** switches the generated pulses to the appropriate electrode(s) of electrode array **150**, for delivery of the current pulse to the tissue surrounding the selected electrode(s). Measurement circuitry **128** is configured to capture measurements of neural responses sensed at sense electrode(s) of the electrode array as selected by electrode selection module **126**.

FIG. 1c is a schematic illustrating interaction of the implanted stimulator **100** with a nerve **180**, in this case the spinal cord however alternative embodiments may be positioned adjacent any desired neural tissue including a peripheral nerve, visceral nerve, parasympathetic nerve or a brain structure. Electrode selection module **126** selects a stimulation electrode **2** of electrode array **150** to deliver an electrical current pulse to surrounding tissue including nerve **180**, and also selects a return electrode **4** of the array **150** for stimulus current recovery to maintain a zero net charge transfer.

Delivery of an appropriate stimulus to the nerve **180** evokes a neural response comprising a compound action potential which will propagate along the nerve **180** as illustrated, for therapeutic purposes which in the case of a spinal cord stimulator for chronic pain might be to create paraesthesia at a desired location. To this end the stimulus

electrodes are used to deliver stimuli at 30 Hz. To fit the device, a clinician applies stimuli which produce a sensation that is experienced by the user as a paraesthesia. When the paraesthesia is in a location and of a size which is congruent with the area of the user's body affected by pain, the clinician nominates that configuration for ongoing use.

The device **100** is further configured to sense the existence and intensity of compound action potentials (CAPs) propagating along nerve **180**, whether such CAPs are evoked by the stimulus from electrodes **2** and **4**, or otherwise evoked. To this end, any electrodes of the array **150** may be selected by the electrode selection module **126** to serve as measurement electrode **6** and measurement reference electrode **8**. Signals sensed by the measurement electrodes **6** and **8** are passed to measurement circuitry **128**, which for example may operate in accordance with the teachings of International Patent Application Publication No. WO2012155183 by the present applicant, the content of which is incorporated herein by reference.

FIG. **2a** illustrates the typical form of an electrically evoked compound action potential of a healthy subject. The shape of the compound action potential shown in FIG. **2a** is predictable because it is a result of the ion currents produced by the ensemble of axons generating action potentials in response to stimulation. The action potentials generated among a large number of fibres sum to form a compound action potential (CAP). The CAP is the sum of responses from a large number of single fibre action potentials. The CAP recorded is the result of a large number of different fibres depolarising. The propagation velocity is determined largely by the fibre diameter. The CAP generated from the firing of a group of similar fibres is measured as a positive peak potential P1, then a negative peak N1, followed by a second positive peak P2. This is caused by the region of activation passing the recording electrode as the action potentials propagate along the individual fibres. An observed CAP signal will typically have a maximum amplitude in the range of microvolts.

The CAP profile takes a typical form and can be characterised by any suitable parameter(s) of which some are indicated in FIG. **2a**. The positions and amplitudes of the peaks can for example be used alone or in combination to generate a correlation between them and the state and severity of a central nervous system (CNS) disorder. Depending on the polarity of recording, a normal recorded profile may take an inverse form to that shown in FIG. **2a**, i.e. having two negative peaks N1 and N2, and one positive peak P1.

FIG. **2b** illustrates how the CAP manifests in the recording, when using a differential recording arrangement with an epidural ground. In FIG. **2b** a normal ECAP shape (A) is inverted and delayed by the propagation distance to the epidural ground electrode (B), and so the differential measure will look like the envelope of C. FIG. **2c** shows the corresponding manifestation in relation to an anomalous CAP (D). The anomalous CAP has a strong doublet, which is inverted and delayed by the propagation distance to the epidural ground electrode (E), and so the differential measure will look like the envelope of F. As shown in FIG. **2c**, and also being the case for FIG. **2b**, the actual recording obtained typically does not include the first positive peak as it is obscured by the stimulus.

The present invention thus recognises that the shape or profile of the compound action potential reflects changes in the ion channel characteristics as a result of pathological or natural change.

Comparison of ECAP measurements from the dorsal column of a number of different human subjects was undertaken in order to identify systematic differences which relate to either genetic or pathological differences between subjects. Measurements of dorsal column evoked compound action potentials show distinct differences between the ECAP shapes measured at different electrodes along the array.

FIG. **3** shows a "normal" ECAP, being a triphasic P1, N1, P2 response, as obtained from "patient 25". The use of epidural ground inverts the N1 at a time when the response passes the ground electrode. As the recorded response of FIG. **3** exhibits no significant abnormalities as compared to the predicted response of FIG. **2**, Patient 25 can be diagnosed as having no measurable neuropathic disease.

In contrast, FIG. **4** shows data from patient 34, measured in both the orthodromic and antidromic directions at respective electrodes either side of the stimulus electrode, each spaced apart from the stimulus electrode by three electrodes. The N1 peak **402** is broader in the orthodromic direction, displays a faster rise time and is larger in amplitude. Moreover, an additional lobe **404** has emerged in the orthodromic response, in deviation from the expected response of FIG. **3**. Any or all of these abnormalities may be detected and/or quantified in order to produce an automated diagnosis of the existence or severity of neural disease in patient 34. For example in some embodiments a measurement may be taken of the signal amplitude or power occurring within a time window covering the anomalous peak **404**. When the amplitude or power in such a time window exceeds a threshold the response may be flagged as being anomalous.

FIG. **5** illustrates the recordings of the corresponding orthodromic and antidromic responses arising from patient 22. As seen at **502** in the N1 peak of the orthodromic response, the N1 peak **502** is broader in the orthodromic direction, displays a faster rise time and is larger in amplitude. An additional lobe **504** has emerged in the orthodromic response, in deviation from the expected response of FIG. **3**. Thus patient 22 exhibits doublets which may be detected and/or quantified in order to produce an automated diagnosis of the existence or severity of neural disease in patient 22.

FIG. **6** is a histogram of N1 peak latencies in ms, measured at the same stimulus electrode to recording electrode separation, for a large number of patients. This illustrates that N1 peak latency is predictable within quite a narrow time range as the peaks have quite a narrow spread over a large number of patients.

FIG. **7** shows the normalised antidromic responses from three patients plotted together. The N1 peaks have very similar latencies. The peak shapes **702** and **704** are normal, noting the effects described in relation to FIGS. **2b** and **2c**.

FIG. **8** shows an example of a large doublet response in the antidromic response of one patient, illustrating that severity of the neural state can be distinguished, for example by comparing the normalised height of lobe **804** to say lobe **404** or **504**.

To explore the question of ectopic discharge, the refractory period was investigated using the "masker probe" techniques set forth in International Patent Application Publication No. WO2012/155189, the contents of which are incorporated herein by reference. FIG. **9** is a plot of the normalized masker probe results for 3 patients, denoted patient nos 16, 19 and 35 respectively. For patient 35 the masked amplitude was divided by the unmasked amplitude. To allow for differences in the measurement mode for

patients 16 and 19, the results were normalized against the responses at ~5000 micro seconds inter-stimulus interval (ISI). In general the results are consistent between patients. As shown in FIGS. 10-12, the CAP profile of patient 35 had the largest double peaks or doublets of the three patients, and also at short ISI's of the order of 100-200 us patient 35 had the largest additional recruitment as indicated at 902. The data for patient 16 was collected with an 80 us pulse width, and so this will affect the additional recruitment at the short ISI's.

FIG. 10 illustrates the progression of CAP profile as the CAP travels away from the stimulus site, for patient 35. This indicates that the existence of an atypical CAP profile may best be detected by making recordings very close to the stimulus site. It is noted that the anomalous peaks propagate with distance, which indicates that they are neural responses from the same group or class of fibres. FIG. 11 shows a response obtained from patient 16, and FIG. 12 shows a response obtained from patient 19, revealing that of these three patients Patient 35 has the most severe doublet formation in their neural response.

There appears to be little consistency between the N1 latency and the appearance of the double response so N1 latency may not be a suitable parameter for diagnosing neural state.

Some embodiments may provide for repeated assessment of the recorded response profile from time to time, for example throughout administration of a therapy, in order to assess disease state, disease progress, and therapy efficacy, and may be used to guide therapy modifications and optimisation over time. Therapy modifications may include modifications of dosage of a medicament and/or modification of a stimulus regime applied by a spinal column stimulator. FIG. 13 illustrates a control loop by which drug dosage or electrical stimuli dosage is adjusted in a dynamic manner, with the magnitude of the doublet (404, 504) being used as a control variable for a feedback loop.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

The invention claimed is:

1. A method of assessing a neural state of a subject, the method comprising:
 - obtaining a recording of a compound action potential arising in neural tissue of the subject from one or more implanted sense electrodes of an implantable neurostimulator;
 - providing to a processor of a control device the recording of the compound action potential;
 - processing, by the processor, the recording to detect an anomaly in a profile of the recorded compound action potential by determining whether a peak in the recorded compound action potential has an atypically swift rate of rise;
 - generating, by the processor, an indication regarding the neural state of the subject based on detected anomalies in the recorded compound action potential;
 - outputting, by the processor, the indication regarding the neural state of the subject; and
 - configuring, by the processor, the implantable neurostimulator using the indication regarding the neural state of the subject.
2. The method of claim 1 wherein the detection of an anomaly in the profile of the recorded compound action

potential further comprises determining whether more than three peaks exist in the recorded compound action potential.

3. The method of claim 1 wherein the detection of an anomaly in the profile of the recorded compound action potential further comprises determining whether a peak in the recorded compound action potential is unexpectedly broad.

4. The method of claim 1 wherein the detection of an anomaly in the profile of the recorded compound action potential further comprises determining whether anomalous frequency components exist in the recorded compound action potential when assessed in the frequency domain.

5. The method of claim 1 wherein the detection of an anomaly in the profile of the recorded compound action potential further comprises:

- determining a degree of deviation of the profile of the recorded compound action potential from a predefined expected compound action potential profile; and
- comparing the degree of deviation with a predetermined threshold.

6. The method of claim 1 wherein the detection of an anomaly in the profile of the recorded compound action potential comprises identifying a locus of neuropathic pain by applying stimuli to first and second neural sites and determining which stimulus gives rise to greatest anomalies in a recorded compound action potential profile.

7. The method of claim 1 wherein configuring the implantable neurostimulator is performed intra-operatively to effect electrode array implantation site optimisation.

8. The method of claim 1 wherein configuring the implantable neurostimulator is performed during a programming stage in order to optimise electrode selection.

9. The method of claim 1 wherein configuring the implantable neurostimulator is performed intra-operatively during a sympathectomy procedure, in order to provide an intra-operative progressive indication of efficacy of the sympathectomy.

10. The method of claim 1, further comprising administering or modifying a therapy in a manner responsive to the indication regarding the neural state of the subject.

11. A neural state measurement system, comprising:

- an implantable neurostimulator, comprising:
 - at least one implantable sense electrode;
 - a telemetry module;
 - a module controller; and
 - a memory, where the memory comprises a control program capable of directing a processor to:
 - obtain a recording of a compound action potential arising in neural tissue of a subject using the at least one implantable sense electrode; and
 - provide the recording of the compound action potential to a processor of a control device; and

the control device, where the processor of the control device is configured to:

- process the recording to detect an anomaly in a profile of the recorded compound action potential by determining whether a peak in the recorded compound action potential has an atypically swift rate of rise;
- generate, based on detected anomalies in the recorded compound action potential, an indication regarding the neural state of the subject;
- output the indication regarding the neural state of the subject; and
- configure the implantable neurostimulator using the indication regarding the neural state of the subject.

12. The neural state measurement system of claim 11, wherein the detection of an anomaly in the profile of the

recorded compound action potential further comprises determining whether more than three peaks exist in the recorded compound action potential.

13. The neural state measurement system of claim 11, wherein the detection of an anomaly in the profile of the recorded compound action potential further comprises determining whether a peak in the recorded compound action potential is unexpectedly broad.

14. The neural state measurement system of claim 11, wherein the detection of an anomaly in the profile of the recorded compound action potential further comprises determining whether anomalous frequency components exist in the recorded compound action potential when assessed in the frequency domain.

15. The neural state measurement system of claim 11, wherein the detection of an anomaly in the profile of the recorded compound action potential further comprises:

determining a degree of deviation of the profile of the recorded compound action potential from a predefined expected compound action potential profile; and comparing the degree of deviation with a predetermined threshold.

16. The neural state measurement system of claim 11 wherein the detection of an anomaly in the profile of the

recorded compound action potential comprises identifying a locus of neuropathic pain by applying stimuli to first and second neural sites and determining which stimulus gives rise to greatest anomalies in a recorded compound action potential profile.

17. The neural state measurement system of claim 11, wherein configuring the implantable neurostimulator is performed intra-operatively to effect electrode array implantation site optimisation.

18. The neural state measurement system of claim 11, wherein configuring the implantable neurostimulator is performed during a programming stage in order to optimise electrode selection.

19. The neural state measurement system of claim 11, wherein configuring the implantable neurostimulator is performed intra-operatively during a sympathectomy procedure, in order to provide an intra-operative progressive indication of efficacy of the sympathectomy.

20. The neural state measurement system of claim 11, wherein the processor of the control device is further configured to administer or modify a therapy in a manner responsive to the indication regarding the neural state of the subject.

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